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GASTRIC TUMOURS OF NEUROGENIC ORIGIN

By ROLAND NIELSEN and M. EIKEN

As early as 1899, Askanazy described an isolated gastric tumour which he considered to have originated from the myenteric plexus. It was not until 1908 and 1910, however, that neurogenic tumours were delimited in more detail pathologically by Verocay, who termed these tumours neurinomata. The terms proposed by Masson (1932) and Stout (1935), schwannoma and neurilemmoma, respectively, appear, however, to be more adequate as such tumours are most frequently presumed to originate from the sheath of Schwann and thus do not contain nerve fibres. Several authors have proposed more detailed subdivision of these nervesheath tumours but hitherto no agreement regarding terminology has been reached.

These tumours may be encountered wherever there are nerves with neurilemma, and may thus occur in the internal organs also, where they most frequently originate from the autonomic nervous plexuses.

The first reliable report of a gastric tumour of neurogenic origin was presented by Picquet in 1922. In Denmark, the first case was reported by Djørup & Okkels in 1927 and since then several studies on the subject, of Scandinavian origin, have been published (Harild 1930, Lagergren & Sjövall 1942, Forssman 1943, Grønbæk 1952, Dahl-Iversen 1959 and others). These studies were primarily concerned with the pathology and clinical findings.

PATHOLOGY

According to recent investigations, benign tumours are stated to comprize 10—15 per cent of all gastric tumours. Of the benign tumours, between five and ten per cent are of neurogenic origin (Ronzini 1934, Minnes & Geschickter 1936, Feyrter 1948, Palmer 1951, Hottinger 1957).

Neurogenic tumours in the stomach occur with almost equal frequency in males and females. As a rule, they are solitary and only extremely rarely occur together with Recklinghausen's disease (Spühler 1935, Palmer 1951).

Pathologically, the tumour concerned is a slowly-growing well-delimited tumour, as a rule, globular or ovoid. The surface is smooth, occasionally slightly lobulated, and covered with normal freely-mobile mucous membrane. Characteristically such tumours are frequently ulcerated. As the blood supply is usually poor, ulceration is most frequently due to necrosis with perforation into the stomach (Odquist 1937, Canney 1948, Dick 1950). Where large tumours are concerned, it is possible, as recorded by v. Braunbehrens (1943), that decubital ulceration may occur on account of the tension on the mucous membrane.

The tumour may extend intramurally, endogastrically or exogastrically, but in a number of cases it grows both endo- and exogastrically and may assume an hour-glass shape with a constriction corresponding to the stomach wall. Gosset (1924) found considerable preponderance of the exogastric type but review of a series of more recent studies, the authors' own cases being included, revealed 81 endogastric, 14 intramural and 38 exogastric and this is in agreement with Palmer's account from 1951.

The tumour may be encountered anywhere in the stomach, but it has been most frequently demonstrated in the body and here particularly along the lesser curvature. The histological differential diagnosis may cause considerable difficulty and, previously, the tumour was frequently confused with sarcomata (Gosset 1924) or leiomyomata (Feyrter 1948).

Malignant degeneration is stated to occur in up to 10 per cent of the cases (Feyrter 1948, Tate & Fusaro 1948, Banks 1950). In Spühler's opinion, the malignant tumours originate from more immature cells.

CLINICAL FINDINGS

Many cases are symptom-free and are diagnosed incidentally at operation or autopsy. Occasionally, tumours may become so large that they can be palpated but they rarely cause obstruction. A frequent symptom is prolonged, uncharacteristic

From The Department of Radiology, Copenhagen County Hospital, Gentofte, Denmark. (Heads: *E. de Fine Licht* and *Olaf Petersen*).

dyspepsia with ulcer pain in exceptional cases. Cachexia does not occur. The most important symptom is haemorrhage which has been demonstrated in up to 80 per cent of the patients (Mondor et al. 1941, Canney 1948). In numerous cases, the haemorrhage is occult (Feldman 1948, Frercks 1953) but, occasionally, haemorrhage endangering life may occur.

RADIOGRAPHIC FINDINGS

Lesser exogastric tumours can scarcely be diagnosed in vivo, even with meticulous radiographic examination. Similarly, with the larger and possibly palpable exogastric tumours, it is, as a rule, difficult to determine the connection with the stomach unless there is degeneration with necrosis into the stomach (Lagergren & Sjövall 1942). In larger exogastric tumours a funnel-shaped dilatation of the gastric wall may occasionally be demonstrated. This is produced by the tension of the pedicle of the tumour (v. Braunbehrens 1943). Dessecker (1922) recommended the use of pneumoperitoneum while Mogena & Pleguezuelo (1959) mentioned pneumogastrography and parietography as diagnostic aids.

In the endogastric forms, the tumour will present on ordinary X-ray examination as a greater or lesser filling defect in the radio-opaque material in the stomach. A regular and smooth outline together with demonstration of a punched-out niche are characteristic but not pathognomonic of benign tumours. It is, similarly, characteristic both for neurogenic tumours and for other benign tumours in the stomach that there is no stiffness of the stomach wall. The folds in the mucous membrane are intact and may frequently be observed to course regularly down around the tumour. The mobility of the stomach wall is retained in contrast to the findings in the majority of cases of malignant gastric tumours.

Although there are thus quite good criteria for differentiation between benign and malignant gastric tumours, it may frequently be difficult to evaluate these conditions by ordinary X-ray examination. In cases with small benign gastric tumours, the retained mucous membrane folds and the normal mobility may cause the tumour to be overlooked.

In The Copenhagen County Hospital in Gentofte, the authors have recently observed four histologically verified and representative cases of gastric tumours of neurogenic origin. These were all investigated both by means of routine X-ray examination and by double-contrast technique (Eiken 1958). It will be demonstrated how the latter method of investigation can, in some cases at any rate, give more exact information and thus increase the possibilities of establishing a specific diagnosis.

CASE HISTORIES

1) Male aged 28 years. Previous health good. Hospitalized on account of uncharacteristic dyspepsia for six months. Laboratory investigations and X-ray examination undertaken 5½ months previously did not reveal anything abnormal. On repeated X-ray examination of the stomach employing the double-contrast technique, a tumour 4×1.5 cm in the stomach wall was found apparently intramurally on the greater curvature. The mucous membrane folds continued over the surface of the tumour and there was no visible ulceration. As the appearance together with the complete retention of the elasticity of the stomach wall suggested a benign tumour, extirpation of the tumour was undertaken. The tumour was the size of a walnut and situated submucosally. Histological examination of a frozen specimen during the operation suggested leiomyoma but closer histological examination proved the tumour to be a neurinoma without signs of malignancy.

2) Female aged 53 years. No previous gastric symptoms. Periodic sensation of pressure in the epigastrium unrelated to meals for six months. Only one episode

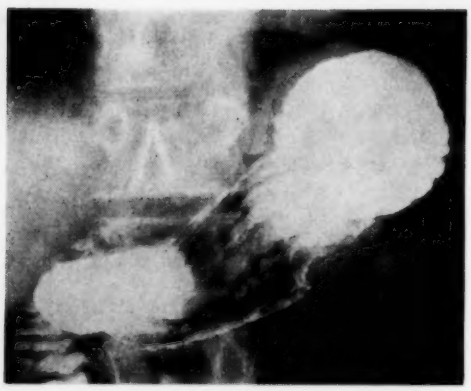


Figure 1.

Case 1: Ordinary X-ray Photograph of the Stomach. Tumour Visible in the Partially Air-filled Stomach.

Figure 2.

Case 1: Examination Employing Double-contrast Technique. The Tumour is Distinctly seen Inferiorly on the Greater Curvature.

of vomiting and no other complaints. Laboratory investigation showed normal values. The stools were not examined for blood. Ordinary X-ray examination of the stomach revealed a filling defect the size of a cherry in the antrum. Supplementary examination using double-contrast technique revealed this to be a broad-based, smooth-outlined polypoid tumour. The remainder of the stomach was normal. On resection of the stomach, a projection, one cm in diameter, was found. Histological examination showed this to be a neurilemmoma situated in the submucosa. There were no signs of malignancy.

3) Male aged 49 years who 45 years old had been submitted to operation for cancer of the sigmoid colon. During the past three years, the patient had experienced repeated attacks of melena and anaemia. X-ray examination revealed a filling defect the size of a tangerine superiorly in the body of the stomach. On control examination employing the double-contrast technique approximately eight weeks later, the tumour appeared to have grown. At this examination, it presented as a broad-based polypoid tumour originating from the anterior wall of the stomach. The surface was more or less regular and smooth. At one point only there was a lesser irregularity which was suspected to be an ulceration. On x-ray examination, the tumour appeared to be benign. On reviewing x-ray photographs from two years previously, it was possible to demonstrate a filling defect the size of a walnut which had not been recognized.

The radiographic findings were verified on transverse resection of the stomach. The mucous membrane

Figure 4.

Case 3: Antero-posterior Exposure of the Stomach Using Double-contrast Technique. The Large Tumour is seen to Reach the Lesser Curvature.

Figure 3.

Case 3: Relief Investigation. The Stomach is Contracted on a Tumour in the Upper Part of the Body of the Stomach.

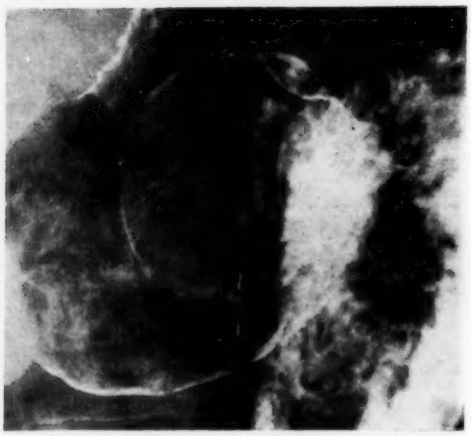
Figure 5.

Case 3: Lateral Exposure of the Stomach Using Double-contrast Technique. The Tumour is seen to Arise from the Anterior Wall of the Stomach.

Figure 6.

Case 4: Ordinary X-ray Photograph of the Stomach. The Tumour Presents as a Large Filling Defect.

was found to be adherent at an isolated point on the surface of the tumour which was the size of a hen's egg. This probably corresponded to the irregularity on the surface observed radiologically. On excision of this region a blood-filled cavity was opened. Histological examination: Neurinoma with no signs of malignancy.



Figures 7 a and b.

Case 4: a. Antero-posterior Exposure b. Oblique Exposure Employing Double-contrast Technique. Supero-laterally an Irregularity is seen on the Surface of the Tumour. This is Probably an Ulcer.

4) Male aged 79 years, admitted with decompensated heart disease and severe anaemia which had been present for two months. No dyspepsia had been present but there was marked melena.

Ordinary X-ray examination showed a filling defect the size of a tangerine in the middle of the body of the stomach. On examination with double-contrast technique, a globular tumour 6 cm in diameter was demonstrated originating from the greater curvature. A little depression on the surface was observed which was probably ulceration. The surrounding stomach wall showed normal elasticity. On the basis of the radiographic findings, it was considered most probable that a benign tumour was concerned and, on account of the ulceration, the diagnosis of neurinoma was considered to be probable.

Partial resection of the stomach was undertaken, the tumour being excised at a distance of approximately two cm from the base. The tumour was the size of a little apple with two areas of ulceration in the otherwise normal mucous membrane. The tumour had grown through the muscular layer and projected slightly on the external surface of the stomach. Histological examination: *Malignant* neurinoma.

DISCUSSION

Neurogenic gastric tumours comprize approximately one per cent of all tumours of the stomach. The clinical picture, as in the case histories reported here, is characterized by striking absence of subjective symptoms. The most dominant symptom is haemorrhage which may occasionally be so violent that severe anaemia results.

It may frequently be difficult on ordinary X-ray examination of the stomach to demonstrate the characteristic features of benign gastric tumours for differential diagnosis. Investigation employing the double-contrast technique has proved to be of value in this respect. In this investigation, the patient receives one or two mouthfuls of thick colloidal barium sulphate. By subsequent insufflation of varying quantities of air and X-ray photography in various projections, it is possible to demonstrate with great accuracy alterations in the elasticity of the stomach wall, so that even minor areas of induration appear distinctly. As the radio-opaque material, as a rule, adheres well to the surface of the tumour, much better reproduction of its appearance, shape and limits is obtained.

Reliable radiographic differentiation between various forms of benign tumour is, obviously, impossible as not only the macroscopic but also the histological differential diagnosis may still cause difficulties. On the other hand, demonstration of one a few well-delimited areas of ulceration in the otherwise smooth outline of a tumour is very suggestive evidence of neurogenic origin, although ulceration may also be encountered in other benign tumours. Even if a specific diagnosis is not

possible, the investigation technique recorded together with an accurate description of the tumour will facilitate planning of a limited surgical intervention such as enucleation, excision or transverse resection. Such limited intervention is of considerable significance in tumours in the vicinity of the cardiac region.

SUMMARY

Four cases of solitary gastric tumour of neurogenic origin, one of which was malignant, are reported. In connection with a brief review of the pathology and clinical features of the neurogenic gastric tumours, the differential diagnostic criteria are mentioned, particular stress being laid on the radiographic diagnosis. Reliable differential diagnosis is impossible but radiographic investigation employing the double-contrast technique permits considerably more accurate evaluation of the appearance and extent of the tumour than ordinary radiographic examination and, in this manner, increases the possibility for differentiating between benign and malignant gastric tumours.

SUMMARIO

Roland Nielsen e *M. Eiken:* TUMORES GASTRIC DE ORIGINE NEUROGENIC

Es reportate quatro casos — le un maligne — de tumores gastric de origine neurogenic. In connexion con un breve revista del pathologia e tractos clinic de tumores gastric neurogenic on mentiona le criterios del diagnose differential con emphase al diagnose radiographic. Es impossibile un definite diagnose differential. Tamen un examination radiographic a contrasto duple permitte un evalutation del apparentia e extento del tumor considerabilemente plus exacte que 10 face un examination ordinari, e talmente illo augmenta le possibilitate del differentiation inter tumores gastric benigne e maligne.

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ON RESECTABILITY OF CARCINOMA OF THE STOMACH

By B. TRÄFF and M. ANDREASSEN

The resectability of carcinoma of the stomach is generally understood in this country as that percentage of all cases hospitalized in which it proves possible to remove the tumour. During recent years, this frequency of resection has increased steadily in the series published, from 20 per cent (Aage Nielsen & Sejer Hansen 1942) to 47 per cent (Andreassen 1958).

The same conditions hold true in an investigation concerning all cases of cancer of the stomach in Denmark in 1943—54, undertaken by The Cancer Registry (Table 1).

The increase in the frequency of resection may be explained partly by improved operative technique and partly by the fact that the patients, on the whole, have sought treatment earlier.

It must, however, be emphasized that the frequency of resection in the series mentioned above does not bear any reasonable relationship to the five-year survival rate (table 2).

Thus, the material of 451 patients treated during the period 1945—1955 in The Departments of Surgery C, D and R, Rigshospitalet, showed, as mentioned previously, a frequency of resection of 47 per cent while the five-year survival rate was only 16 per cent. This suggests that this frequency of resection was estimated solely by whether the tumour could be removed and the continuity of the intestine be re-established; whether tumour tissue was left in the resection surfaces or in the regional glands was not taken into consideration. Correspondingly, palliative operations comprised only 11 per cent of the material.

Since 1956, in Department D, microscopic examination of frozen sections has been employed extensively during the operation, and cases were only considered to be radically operable when such microscopic examination confirmed that the resection surfaces were free from tumour growth and that the glands, with the exception of the glands along the curvatures in the immediate vicinity of the tumour, were similarly free from tumour tissue.

In a few of the patients submitted to operation at the commencement of this period, microscopic examination of frozen preparations was not undertaken to the same extent as later. In the authors' opinion, however, the investigation was sufficiently comprehensive to permit classification according to the principles mentioned above.

Table 3 shows how the various groups are distributed in a five-year material consisting of 124 cases treated in Department D in 1956—1961. The table shows that five patients were *not submitted to operation*. Two of these patients died prior to operation (thrombosis of the pulmonary artery and cardiac disease). The diagnosis of cancer of the stomach was confirmed at autopsy.

The remaining three patients in this group were not submitted to operation on account of cachexia, jaundice and palpable tumour masses in the abdomen. The diagnoses were established from the clinical findings supplemented by radiographic examination.

Exploratory laparotomy alone was performed in 41 patients, because metastases to the liver, carcinosis of the peritoneum, or tumour invasion in regions rendering removal impossible were found at operation. In numerous cases of this nature, not even gastroenterostomy was undertaken to relieve any symptoms of obstruction, as experience has shown that such attempts seldom relieve the patients but most frequently increase the mortality (Pack).

Palliative operation was carried out in 57 patients. By this is understood that the tumour was removed and the continuity of the intestine re-established but that tumour tissue (in glands

From The Department of Surgery D (Professor *E. Husfeldt)*, Rigshospitalet, University of Copenhagen, Denmark.

Table 1.

Patients with Cancer of the Stomach in Denmark 1943—1954. Total Number and Number of Cases in Which Macro-radical Resection was Carried out. The Percentages Indicate the Incidence of Resection.

(Reproduced by courtesy of *B. L. Sørensen)*.

	1943-1947		1948-1952		1952-1953	
Males	507/3012	16.8 %	1002/3424	29.3 %	454/1398	32.5 %
Females	311/1981	15.7 %	555/2115	26.2 %	254/848	30.0 %

Table 2.

Material from 1945—1955 (Rigshospitalet, Departments C + D + R).

Total material: 451.

	No operation	Exploratory laparotomy	Palliative operation	Macro-radical operation
No.	41	147	52	211
Percentage	9%	33%	11%	47% (= resectability)

Table 3.

Material from 1956—1961 (Rigshospitalet, Department D).

Total material: 124.

	No operation	Exploratory laparotomy	Palliative operation	Micro-radical resection
No.	5	41	57	21
Percentage	4%	33%	46%	17% (= resectability)

or in the resection surfaces) was left behind. This group is large and forms 46 per cent of the material.

The group includes the cases which would have been regarded as treated radically, if microscopic examination had not been employed, but in which microscopy of frozen sections revealed tumour tissue which could not be removed (in the resection surfaces or in glands). Further, this group contains all the cases in which the tumour was removed although it was obvious to the naked eye that tumour tissue was left behind. This procedure has been employed to an increasing extent on the basis of the experience, also shared by others (Berkson), that even if tumour tissue is left, *removal of the tumour* results in a more tolerable existence but does not prolong the period of survival.

Micro-radical resection was undertaken in 21 patients. In these patients, microscopic examination confirmed that no tumour tissue was left in the resection surfaces and no metastases were found in the lymph glands elsewhere than in the immediate vicinity of the tumour, *viz.*, corresponding to the greater and lesser curvatures. The incidence of micro-radical resection was thus 17 per cent.

Out of these 21 patients, two had cancer in the pre-pyloric part and nine had tumours which were diagnosed microscopically as ulcer cancers, while the tumours in the remaining ten cases were localized to the body of the stomach or to the cardiac region.

SUMMARY

In this country, macroscopic criteria have hitherto been used to estimate whether operation has been radical. The frequency of radical resection thus found bears no reasonable relationship to the five-year survival, as the figure includes cases in which, according to our present criteria, tumour was in fact only removed palliatively.

The frequency of *micro-radical* resection shows better agreement with the number of five-year survivors. This figure, therefore, would appear to be a more realistic expression for the resectability of carcinoma of the stomach.

SUMMARIO

B. Träff e M. Andreassen: LE RESECTABILITATE DE CARCINOMA DEL VENTRICULO

Es presentate evidentia statistic pro demonstrar, que ex tote casos de cancere del ventriculo hospitalisate le percentage correspondente al resectiones »radical« basate super criterios macroscopic non tene ulle relation rationabile al rata de superviventia de cinque annos. Le causa de iste facto debe esser le includer de casos ubi le tumor ha essite extirpate solmente palliativemente, secundo nostre criterios al presente.

Dunque il es plus correcte considerar multo minor le percentage de resection radical basate super criterios microscopic, lo que corresponde multo melio al numero de patientes supervivente post cinque annos.

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AUTOPSY FINDINGS IN A CHILD WITH INFANTILE SPASMS AND HYPSARRHYTHMIA

WITH A SURVEY OF THE EFFECT OF ACTH

By JENS PALUDAN

Infantile spasms with hypsarrhythmia have been studied lately with increasing interest, especially since several reports (Low 1958, Hansted & Thygesen 1958, Sorel & Dusaucy-Bauloye 1958, Gastaut et al. 1959, Trojaborg & Plum 1960, Brandt & Melchior 1960, Kiørboe & Damgaard 1960), have described improvement and even recovery from this type of epilepsy following treatment with corticotropin (ACTH) and glucocorticosteroids (prednisone). The results of this therapy have caused a discussion about the etiology and pathogenesis, and a series of theories have been advanced.

It was the report by Christensen & Melchior (1960) about the pathological findings in the brains of six patients with infantile spasms and hypsarrhythmia that first suggested a pathogenesis, because prior to this the pathological findings of only one case had been carefully studied and published by Bamberger & Matthes (1959) who found localized microgyria with arrest of development of cortical neurons and perivascular gliosis. In a paper by Poser & Low (1960) the post mortem findings in three children with infantile spasms were reported. It is not described, however, if electroencephalographic findings typical to hypsarrhythmia were seen in these cases. In one case a chronic edema and spongy degeneration of the grey matter in the hemispheres and the brain stem were found. In the second case similar changes were found diffusely within the white matter of the hemispheres, the cerebellum and the brain stem, with a varying degree of demyelinisation and decreased number of Purkinje cells. Finally, the third case presented similar abnormalities, but in this case they were present in the grey as well as the white matter.

On the basis of the pathological findings Christensen & Melchior conclude that infantile spasms with hypsarrhythmia is not a disease *per se* but a syndrome occurring in

(1) degenerative cerebral processes (microcephalia, hydrocephalus, porencephalia and/or severe gliosis) due to exogenic causes such as infections during pregnancy and birth injuries.

(2) dysplastic abnormalities such as arrested development of the ganglion cells in the cerebral cortex and the cerebellum, delayed myelinisation but only slight or no degenerative changes at all. These changes are presumed to be caused by "inborn errors of metabolism".

Because the pathological findings of only the above mentioned seven cases have been reported so far, the present case with infantile spasms and hypsarrhytmia is presented.

The patient is one of five children with infantile spasms and hypsarrhythmia who all had repeated electroencephalographic studies and were treated with prednisone or ACTH. The effect of the treatment on the clinical condition and the electroencephalographic changes in these five cases have been published by Kiørboe & Damgaard.

CASE HISTORY

This little girl was only 14 hours old when she was first admitted to the Pediatric Department. Both parents were healthy and the patient was their first child. The mother had been well during pregnancy but the delivery was difficult and lasted for 13 hours and an episiotomy was done. The weight of the baby was 3550 g. The child was without respiration after birth, and artifical respiration with oxygen was given for about one hour, and big amounts of amnion fluid were aspirated from the airways. Eleven hours following birth intermittent cyanosis developed and she was admitted to the pediatric department. During the first two days numerous seizures of tonic-clonic spasms were observed in all extremities, and the patient had irregular respiration and intermittent cyanosis. Within two weeks the condition gradually became normal, and at the time of discharge the patient showed no definite signs of cerebral damage.

At the age of seven months she was admitted again, because she during the past two months had had spells of typical infantile spasms which were observed also during the admission. She was now found to be retarded mentally with impairment of motor control. The head was microcephalic. The EEG showed hypsarrhythmia, and the patient was started on prednisone 10 mg three times daily. Following this treatment the EEG became normal, the seizures ceased, and the patient improved mentally although she was still very retarded and gradually showed signs of the Cushing's syndrome. When the treatment was discontinued the EEG again became abnormal, and the treatment with prednisone was repeated followed by improvement of the condition. At the age of 13 months she was discharged on a daily dosis of 2½ mg of prednisone. The EEG was slightly abnormal but without hypsarrhythmia. At the age of 15 months the child was seen as an out-patient. She still showed signs of marked mental retardation and impairment of motor control, and intermittent hypsarrhythmia was found on the EEG.

From the Pediatric Department (Head: *J. Flamand Christensen)* and the Institute of Pathology (Head: *J. Vesterdal Jørgensen)*, Odense County and City Hospital.

When the child was 17 months old she was admitted because of a high fever and died within two hours due to an acute respiratory infection.

Clinical diagnosis: Encephalopathia atroficans (microcephalia), epilepsia (infantile spasms), oligophrenia.

Autopsy findings: Tracheo-bronchitis acuta, atelectases dispersae pulmonum.

Brain section: Possibly the gyri are smaller than normal in the anterior half of the hemispheres and cortical impressions are found in the parietal lobe and the postcentral region on both sides. Coronal section of the brain revealed a dilatation of the ventricular system and in the subcortical white matter several cysts are noticed in the anterior half of the left hemisphere. There is a generalized atrophy and sclerosis of the white matter and the corpus callosum is only two mm in thickness. The cerebellum appears normal by external examination but both in the cerebellum, the medulla and the pons the tissue shows an increased resistance.

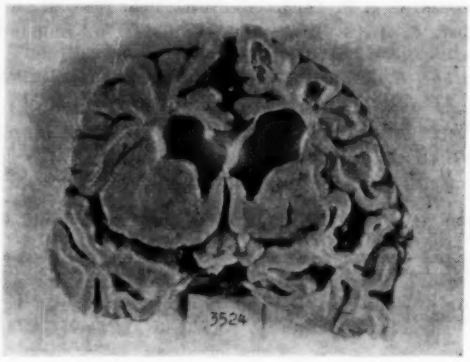

Fig. 1.

Coronal Section of the Brain. Polyporencephalia in the left Hemisphere and Ventricular Dilatation.

Histological examination: In extensive areas of the cortical grey matter the histological examination shows severe subpial gliosis with piloid and fibrillary astrocytes extending in a trabecular fashion through the cortex and alternating atrophy of the ganglion cells that appear, however, to have reached the normal state of maturation and stratification in most places. The abnormal cortical findings are found predominantly in the premotor and motor regions and in the temporal lobes. In the regions of the left hemisphere where cystic degeneration was noticed, glial trabeculars were seen separating cystic cavities with macrophages containing lipoid material. Also in the right temporal lobe and in the striated body small cysts are found with proliferation of glia apparently of different age and in some cases containing macrophages filled with lipoid material. The white substance is markedly atrophic with severe proliferation of the glia to such an extent that large areas only consist of fibrillary astrocytes in varying density. In the internal capsule a fair amount of myelinised nerve fibers are found, but in the corpus callosum and the rest of the white substance only few are present. The myelinisation is incomplete but it can not be established whether this is caused by a defect in the myelinisation or a degeneration. There is a periventricular subependymal severe gliosis. The brain stem and the cerebellum are normal except for slight edema and hyperemia. The leptomeninges over both frontal lobes are edematous with macrophages containing blood and lipoid material but there are no signs of infection neither here nor in the brain substance.

Histological diagnosis: Atrophia cerebri cum polyporencephalia et dilatatione ventriculorum ex anoxia cerebri.

In this case the etiology is obvious as delivery was difficult and the child showed immediate signs of severe asphyxia. Corresponding to this the postmortem examination of the brain revealed pronounced degenerative changes typical of severe anoxia.

EFFECT OF ACTH AND GLUCOCORTICOSTEROIDS

Gastaut et al. believe that infantile spasms with hypsarrhythmia are caused by an encephalitis on a hetero-allergic or auto-allergic basis, and they presume that the clinical and encephalographic effect of ACTH in the case of this disease stems from the fact that this drug has an anti-inflammatory effect. Their theory is supported by reports on the preventive effect of cortisone and the curative effect of ACTH on experimental allergic encephalomyelitis (Kabat et al. 1952, Moyer et al. 1950, Gammon & Dilworth 1953).

Christensen & Melchior believe that only in cases where the infantile spasms are due to delayed maturation of the central nervous system one can expect an effect from ACTH, whereas such an effect should not be expected in cases where the symptoms are due to severe degenerative cerebral lesions.

Field (1955) showed that cortisone decreases the number of micro-glial cells, promotes the maturation of these cells and inhibits their amoeban activity in both human embryoes and young animals. Therefore one could expect an effect on such proliferative glial processes as found in cases of infantile spasms.

Finally the effect of ACTH and glucocorticosteroids on the electroshock seizure threshold should be considered. Both drugs lower a normal threshold and might cause seizures. In the case of ACTH this is probably due to an effect on the adrenal cortex resulting in an outflow of hydrocortisone into the bloodstream. Animal experiences have shown, however, that ACTH and other corticosteroids can normalize a seizure threshold whether it is elevated or lowered (Woodbury 1954).

Infantile spasms with hypsarrhythmia may be interpreted as a reaction of the central nervous

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Brain section and histological examination by Erna Christensen, M. D.

system specific of a certain age and following certain cerebral insults such as perinatal anoxia, depressed maturation due to metabolic disturbances, and finally infectious and toxic cerebral insults to the foetus.

In other words, ACTH and glucocorticosteroids act on the symptom, infantile spasms with hypsarrhythmia, caused by many different cerebral lesions in the infant. As one can hardly expect a curative effect from these drugs on so many different lesions, the effect from ACTH and glucocorticosteroids most likely is due to a direct interference with the cerebral mechanism producing seizures in the case of infantile spasms. At the present time the nature of this influence is unknown.

SUMMARY

The case history and post mortem findings in the case of a child with infantile spasms and hypsarrhythmia treated with prednisone is reported. Following delivery the baby showed severe asphyxia and the post mortem examination of the brain showed marked degenerative changes typical of anoxia. The favourable effect of ACTH and prednisone is discussed and the theory advanced that the two drugs act directly on the mechanism responsible for the seizures in these cases.

SUMMARIO

Jens Paludan: TROVATAS PER AUTOPSIA IN UN NEONATO CON SPASMOS INFANTIL E HYPSARRHYTMIA. *Con un revista super le effecto de ACTH*

Es reportate le anamnese e trovatas postmortal de un neonato con spasmos infantil e hypsarrhytmia tractate per prednisone. Secundo le delivrantia le baby ha monstrate signos de sever asphyxia, e le examination postmortal del cerebro ha revelate marcate e typic alterationes degenerative ex anoxia. Es discutite le effecto favorabile de ACTH e prednisone, e le theoria face verisimile un action directe de ambe drogas super le mechanismo responsabile del convulsiones in iste casos.

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HISTOPATHOLOGY OF THE CORIUM IN OSTEOGENESIS IMPERFECTA

By P. STADIL

Osteogenesis imperfecta is a generalised connective-tissue disease which in addition to the bones involves the teeth, ligaments, fasciae, sclerae, osseous labyrinth and skin. From a clinical point of view, the most characteristic features of this disease are fragility of the bones, impaired hearing, and blue sclerotics. In addition to these three cardinal symptoms there may be a thin, atrophic skin, laxity of the joints, and herniae; all these features are manifestations of a single defect in the connective tissue. As stated by Follis (1953), this defect is apparently localised in the reticulum fibrils, which are not, or only incompletely, differentiated into normal collagenous fibres.

The disease is considered to be inherited as an autosome Mendelian dominant.

Clinically, a distinction is made between a congenital and a tardive type. The congenital type of the disease is so severe that even the slight traumata which the foetus is exposed to in utero result in numerous fractures. The infant is usually stillborn. In the tardive type few symptoms may be present; fractures may not occur, or they occur relatively late in life. The disease may thus sometimes manifest itself by blue sclerotics alone, or by blue sclerotics and impaired hearing (otosclerosis). Seedorf (1949) divided the tardive type into a mild and a severe form. In the latter the tendency to fractures develops during childhood, in the former considerably later in life.

The aforementioned classification of osteogenesis imperfecta into a congenital and a tardive type is artifical and is actually only an expression of the considerable clinical variability of this connective-tissue disease. The basic defect of the connective tissue is the same in the two types, as appears from the following observations (McKusick, 1960): The congenital and tardive forms occur in different members of the same family; there are gradual transitions from one type to the other; and the qualitative histological manifestations are completely identical.

That osteogenesis imperfecta also involves the skin was shown by Follis (1952, 1953), who observed an increased number of reticulum fibrils in the corium which was thinner than normal. Occasionally, he found that the corium was made up exclusively of argyrophilic fibrils, while

From the University Department of Otology (Head: Professor *H. C. Andersen)*, the Experimental Laboratory, the Radium Centre for Jutland (Head: Professor *Carl Krebs)*, and the State Hearing Rehabilitation Centre (Head: *O. Bentzen)*, Aarhus Kommunehospital, Aarhus.

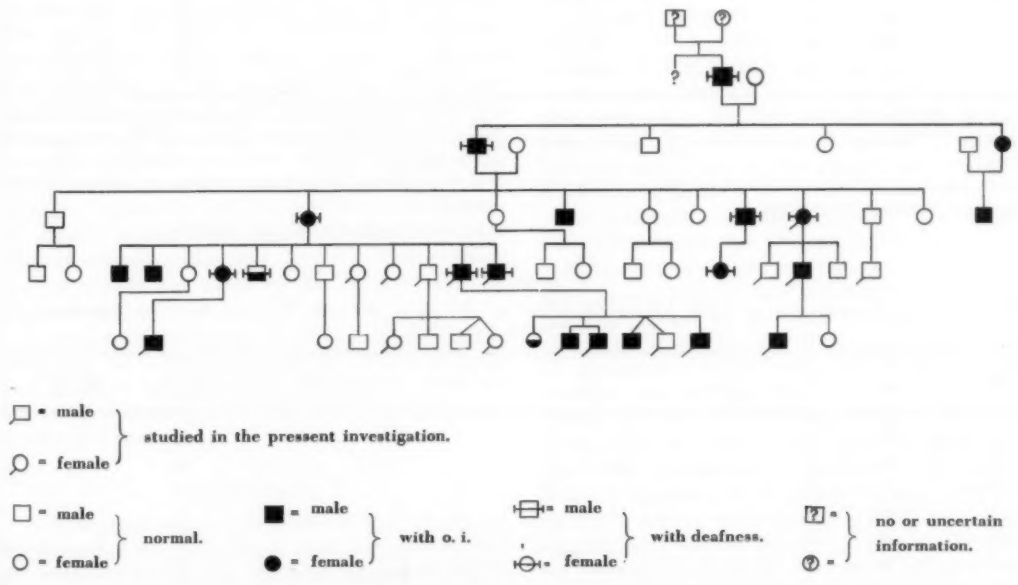

Fig. 1.
Shows the Occurrence of Osteogenesis Imperfecta (o. i.) in the Family.

argyrophobic (*i. e.* "collagen") fibres were completely absent.

PERSONAL INVESTIGATIONS

To extend if possible our knowledge of the histopatology of the corium in osteogenosis imperfecta, I have studied a family in which this disease occurs. This family has previously been studied by Seedorf (1949), in whose monograph it is designated as family No. 53. A total of 17 members of the family were studied; eight were unaffected, and nine had the tardive form of the disease. All nine had blue sclerotics and a pronounced tendency to fractures; complete deafness was present in one (Case 9) and moderate to severe hearing inpairment, mainly of the conductive type, in two (Cases 7 and 8).

Figure 1 shows the occurrence af osteogenesis imperfecta in the family and also indicates the members who were studied in the present investigation.

TECHNIQUE

Biopsy specimens were secured by means of a skin punch (5—7 mm in diameter) from the postero-medial aspect of the upper arm, one handbreadth above the olecranon. The specimens were at once placed in a freshly prepared solution of 4 per cent lead acetate, and then embedded in paraffin and cut into sections of a thickness of 5—7 μ. The following staining methods were employed in all the biopsy specimens studied: —

Haematoxylin-eosin	— general view
van Gieson Hansen	— collagenous fibres
Orcein (Unna)	— elastic fibres
Foot's stain	— reticulum fibrils

and for the evaluation of the ground substance: —

Periodic acid-Schiff (PAS) by the method of McManus.

Toluidine blue by the method of Asboe-Hansen.

HISTOLOGY

As appears from Table 1, the corium was thicker than normal in two, normal in one, questionably thinner than normal in one, and thinner than normal in five.

Table 1.

Results of the Examination of nine Individuals with Osteogenesis Imperfecta.

Case No.	Sex	Age (yrs.)	Co.	E.F.	D.E.F.	R.F.	No. of fractures	Impaired hearing
1	M	9	—	++	++	+	10	
2	M	9	—	++	++	+	10	
3	M	10	—(—)	++(+)	+(+)	(+)	9	
4	M	11	—(—)	++(+)	++	++	6	
5	M	17	+	++	+(+)	++	10	
6	M	40	+	++(+)	++	(+)	6	
7	M	41		+++	++	++	>10	++
8	M	42	(—)	++	++	+	46	+++
9	F	72	———	+++	++(+)	+++	>10	++++

Co., the thickness of the corium as compared with normal; —, thinner than normal; +, thicker than normal.

E. F., number of elastic fibres as compared with normal; +, increased in number.

D. E. F., degeneration of elastic fibres, *i. e.* the fibres are to a variable degree coarse, curled, fragmented and clumped.

R. F., number of reticulum fibrils as compared with normal.

No sign indicates normal finding.

Table 2.

Results of the Examination of Eight Normal Members of the same Family Without Hearing Impairment. For Explanation, see Table 1.

Case No.	Sex	Age (yrs.)	Co.	E.F.	D.E.F.	R.F.	No. of fractures	Impaired hearing
10	M	18					0	
11	F	20	(—)				0	
12	F	20					0	
13	M	35					0	
14	M	43					0	
15	M	45					0	
16	F	49					0	
17	F	57					0	

Hyperelastosis, *i.e.*, an increased number of elastic fibres, associated with signs of degeneration of the fibres, was observed in all nine cases. The number of reticulum fibrils was questionably increased in two and definitely increased in the remaining seven.

It may be added that this hyperelastosis generally involved the entire corium. The degeneration of the fibres also extended throughout the corium, although it was usually most pronounced in the basal part of the reticular layer. The degeneration also involved the normally fine fibres in the papillary layer, which in the patients with osteogenesis imperfecta were either completely absent or seen as short, coarse clumps.

Reticulum fibrils are only sparsely represented in normal skin around sweat glands, vessels and at the junction between the epidermis and corium. In the individuals with osteogenesis imperfecta studied reticulum fibrils were observed throughout the corium, although they were usually densest in the upper third.

After haematoxylin-eosin and van Gieson-Hansen staining, the collagen fibres usually appeared as very thin fibrils arranged in loose whorls without a tendency to formation of the usual wide collagen fibres.

In seven of the nine individuals, sweat glands were present at a high level in the corium, roughly midway between the epidermis and subcutaneous tissue instead of, as usual, in the deeper part of the corium towards its junction with the subcutaneous tissue. In one, the specimen did not contain sweat glands, and in the last case, the sweat glands occupied their normal level.

As assessed by the toluidine-blue and PAS techniques, the ground substance showed abnormalities only in one (Case 9), *viz.*, diffusely increased metachromasia and, possibly, a slightly increased PAS positivity of the papillary layer, which gradually disappeared in the upper part of the reticular layer. This patient also exhibited severe basophilic degeneration of the collagen fibres, especially in the upper third of the corium. These changes might be interpreted as manifestations of severe, senile degeneration of abnormal connective tissue, since this form of degeneration normally does not occur in the corium from unexposed areas.

In the eight unaffected members of the family, who had no signs or symptoms of the disease, and in all of whom normal audiograms were obtained, no histological changes in the corium were observed (Table 2).

DISCUSSION

It is beyond any shade of doubt that the aforementioned nine individuals had osteogenesis imperfecta. As the family has also been thoroughly studied by Seedorf (1949), the correctness of the diagnosis need not be further discussed here.

That the corium in patients with osteogenesis imperfecta is thinner than normal and contains an increased number of argyrophilic fibres has previously been demonstrated by Follis, and the present study merely confirmed his observations.

As far as I know, mention has not previously been made of the changes in the elastic fibres.

It is very unlikely that the disease under consideration should be a combination of osteogenesis imperfecta and the Ehlers-Danlos syndrome. The latter is a rare connective-tissue disease, which is inherited as an autosome Mendelian dominant; its most important symptoms are hyperelasticity of the skin, hyperextensibility of the joints, abnormal fragility of the skin and blood vessels, with formation of atrophic scars and development of pseudo-tumours of the knees, heels and elbows. Histologically, the disease is characterised by degenerative changes in the collagen and elastic tissues. As far as I know, only one well-documented case of the combination of these diseases has been described in the literature (Biering & Iversen 1955).

None of the nine patients exhibited skin changes similar to those seen in the Ehlers-Danlos syndrome. As might be expected, a few of the younger patient studied showed slight hyperextensibility of joints, but not to the extent which is characteristic of the Ehlers-Danlos syndrome.

A combination of osteogenesis imperfecta and pseudoxanthoma elasticum cannot be ruled out. The latter disease is a connective-tissue disease inherited as a recessive character and marked by cutaneous, ocular and circulatory changes. The skin becomes thick, coarse, loose and inelastic with exaggeration of the normal creases and folds. On the skin there are papules and plaques. According to Lever (1954), the histological characteristics of the disease are degenerative changes in the elastic fibres in the central and lower parts of the corium, usually in circumscript areas, in which the fibres are also increased in number, whereas the fibres in the upper part of the corium are normal.

Clinical studies on the eyes and circulation were not performed in the present series.

Skin changes similar to those present in pseudoxanthoma elasticum were not disclosed. The histological changes in the elastic tissue in pseudoxanthoma elasticum and those observed in cases of osteogenesis imperfecta show fairly wide differences. In osteogenesis imperfecta the corium reveals diffuse involvement, including the upper parts, and no cases have been encountered in which the changes were confined to well-defined areas. Blegvad & Haxthausen (1921) described a patient with osteogenesis imperfecta and macular antrophy of the skin, in which histological examination of the involved areas showed atrophic elastic tissue. None of the patients in the present series revealed any such macular atrophy.

For the sake of completeness it should be mentioned that none of the biopsy specimens were taken from scars or milia.

As previously pointed out, the sweat glands were situated at a relatively high level in the majority of the patients, a phenomenon which has previously been reported only in scleroderma in its local or generalised form. None of the patients showed clinical or histological signs of the latter disease. Incidentally, it would have been very surprising and very unlikely that so many members of the same family, and only those with osteogenesis imperfecta should have suffered from this rare condition.

Finally, it should be mentioned that some of the biopsy specimens from the individuals with osteogenesis imperfecta contained a few hair follicles, completely surrounded by normal fat cells, in the upper part of the subcutaneous tissue, in which these are normally absent.

CONCLUSIONS

According to the aforementioned observations the following changes in the corium must be considered to be typical of osteogenesis imperfecta: (1) The corium is thinner than normal; (2) the number of argyrophilic (reticular) fibres is increased; (3) there is also an increased number of elastic fibres showing a variable degree of degeneration; (4) the sweat glands are situated in the upper parts of the corium; and (5) hair follicles are occasionally present in the subcutaneous tissue.

As is seen from Table 1, the connective-tissue changes are unrelated to age and, what is still more interesting, also to the bone stability. A pronounced tendency to fractures was seen in Cases 1, 2, 3, 4, and 8, whereas Cases 5, 6, 7, and 9 had not sustained any fractures since the age of 14 years. Nor was correlation revealed between the severity of the skin changes and the frequency of fractures. Case 4, for example, had had six fractures, while Case 8 had sustained a total of 46 fractures.

Thus it may be expected that the aforementioned qualitative skin changes can also be demonstrated in other patients with osteogenesis imperfecta, even in the mildest forms of the disease in which a tendency to fractures is absent or does not develop until increased decalcification referable to advancing age has occurred. If such a case of osteoporosis of doubtful origin is encountered, the result of a skin biopsy may show whether it is merely a "simple" postmenopausal osteoporosis or an accentuation of a pre-existing osteogenesis imperfecta.

If, as suggested by Wulstein, Ogilvie & Hall (1960), otosclerosis may by legitimately regarded as merely a local form of osteogenesis imperfecta, one might expect to find the abovementioned qualitative histological changes in the corium in patients with otosclerosis.

Finally, it may be mentioned that a study on the corium of patients with otosclerosis has already been performed, and the results, which will be published in a subsequent paper, confirm the assumption just stated. Accordingly, it seems to be justified to assume that a certain pathogenic relationship exists between osteogenesis imperfecta and otosclerosis.

SUMMARY

The histological changes in the corium of nine individuals with osteogenesis imperfecta are described. It is concluded that the following changes are characteristic of this disease: The corium is thinner than normal; the corium contains an increased number of argyrophilic and elastic fibres; the latter fibres show a variable degree of degeneration.

It is noteworthy that identical qualitative histological changes have been demonstrated in the corium of patients with otosclerosis.

SUMMARIO

P. Stadil: HISTOPATHOLOGIA DEL CORIO IN OSTEOGENESIS IMPERFECTE

Es describite le alterationes histologic del corio de nove individuos con osteogenesis imperfecte. Il es concludite que le alterationes sequente es characteristic pro le maladia: Le corio es attenuate. Illo contine un numero augmentate de fibras argyrophilic e elastic. Le ultimes presenta varie grados de degeneration.

Remarcabilemente on ha trovate identic alterationes histologic qualitative in le corio de patientes con otosclerosis.

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A NEW SEROREACTION FOR LUPUS ERYTHEMATOSUS DISSEMINATUS

A COMPARISON BETWEEN THE LATEX AGGLUTINATION TEST (HYLAND) AND THE *LE* CELL PHENOMENON

By ROB. JORDAL & B. STRANDBERG

Since lupus erythematosus was first described in 1828, the delimitation of the disease has undergone considerable changes. This clearly illustrates the difficulties encountered in systematic medicine, when attempting to define the concept "a disease". The first description of the disease was dominated by its dermatological symptoms, and for almost a century it was regarded as belonging to the field of dermatology.

The generalized nature of lupus erythematosus was pointed out by Baehr, Klemperer & Schifrin in 1935. These authors also gave a detailed account of the characteristic histopathology — haematoxylin bodies, "wire-loop" changes in the kidney and periarterial fibrosis of the central arteries of the spleen — and considered the disease in relation to other diseases of unknown aetiology and pathogenesis, such as periarteritis nodosa and scleroderma. However, this did not reduce the diagnostic difficulties for the clinician. It was not until Hargraves demonstrated the LE cell phenomenon (1949) that a decisive contribution was made to certainty of diagnosis, and it was considered for a time that this diagnostic aid would make it possible to delimit the disease and solve the problems of aetiology and pathogenesis.

Serological studies have shown that the LE cell phenomenon is contingent on a serum factor, but that this is only one detail in the antibody mosaic characteristic of lupus erythematosus disseminatus (LED). It is a well known fact that patients with this disease are very active antibody producers; for example, immuno-antibodies have been demonstrated against erythrocytes, leukocytes, thrombocytes and coagulation factors, and against liver, heart and kidney tissue.

The LE serum factor is the best studied of these antibodies, and it is well characterized; it occurs in the 6.6 S proteins in the gamma globulin fraction. It behaves as an antibody, reacting strongly with cell nuclei, presumably in the first instance with their content of DNA-histone. However, the serum of these patients also seems to contain other anti-nuclear globulins; for example, a gamma macroglobulin which is anti-nuclear for liver cells.

From the Central Laboratory (Head: *G. C. Brun)* and the Department of Physical Medicine (Head: *B. Strandberg)*, Copenhagen County Hospital, Gentofte.

It must now be accepted as certain that the LE cell phenomenon is not specific for LED, nor is it sufficiently sensitive to demonstrate all cases of this disease; for one thing, it is really an indirect method of demonstrating the LE serum factor, and for another, the *in vitro* phenomenon in question is subject to the influence of other, unknown factors.

In the field of laboratory diagnosis, therefore, more direct methods of demonstrating this serum factor have been sought. A considerable number of modifications of antigen-antibody reactions are in use at present for this purpose:

(1) Methods in which the anti-nuclear globulins are bound to the cell nuclei, being demonstrated indirectly here:

(a) The anti-human globulin consumption test (AGCT), in which the LE factors are bound to calf thymus nuclei, followed by a measurement of the fall in titer in an added solution of anti-human globulin.

(b) Demonstration of binding of fluorescent anti-human globulin to cell nuclei which have been exposed to serum containing anti-nuclear globulins.

(2) Agglutination reactions between antigen-treated particles and serum containing anti-nuclear globulins:

(a) Latex particles coated with DNA protein.

(b) Latex particles coated with DNA.

(c) Erythrocytes treated with tannic acid and coated with DNA protein.

(d) Bentonite particles coated with DNA.

Most of the above tests are unsuitable for routine use outside specially interested and equipped laboratories, as the antigen suspensions do not keep very well.

However, *Hyland Laboratories* have succeeded in producing stable suspensions of latex particles coated with DNA protein, and in using this for a simple reaction.

It is obviously of great interest to examine the value of such a reaction, both by correlating it with the clinical picture, and by comparing the results with those obtained in the LE cell reaction, the most reliable diagnostic aid so far.

A total of 100 patients were selected for parallel studies on the basis of disease pictures indicating

examination for the LE serum factor. A latex agglutination test was carried out at the same time, irrespective of the result of the LE serum factor test.

PROCEDURE

A. Latex agglutination reaction (LE test).

The latex particles are coated with desoxyribonucleoprotein, produced from calf thymus by the method of Mirsky & Pollister (1946). The reagent is stable when stored at + 4° C. The suspension is shaken thoroughly immediately before use.

One drop of serum from the patient to be examined is placed on a glass slide and mixed thoroughly with one drop of latex suspension using a swab pin. The slide is rocked carefully for two minutes, then the reaction is estimated macroscopically, preferably against a dark background. A positive reaction is shown as an obvious clumping of the particles. Positive reactions have a tendency to weaken after standing for some time. Fresh sera were always examined, but experiments showed that the activity remained unchanged after freezing to — 20° C. All samples were examined by the same person.

B. LE cell reaction.

The method is that given by Zinkham & Conley (1956). The reaction is routinely carried out three days running. It is considered positive if typical LE cells are found even in only one of the preparations. "Nuclear pads" and rosette formations alone are not considered adequate for a positive result.

In all cases, the preparations were evaluated by experienced laboratory assistants, and doubtful reactions were discussed with the medical staff.

MATERIAL

The patient material is obviously very heterogeneous, with a considerable preponderance of women (69 per cent).

A total of 29 positive LE cell reactions were found and three agglutination tests. Ten of the LE cell reactions were found in men and the other 19 in women, corresponding to the composition of the material. The three positive agglutination tests were all demonstrated in women.

The material was divided into six groups, which will be discussed separately.

Group 1 comprises infectious diseases, irrespective of localization and character. The group consisted of 16 patients, seven of whom showed a positive LE cell phenomenon, but there were no cases of positive LE test. The majority of the cases giving a positive cell phenomenon were patients with pulmonary or pericardial disease having a certain similarly to LED. In none of these positive cases was it possible to verify the diagnosis of LED. One particularly suspect case, with combined pneumonia and pericarditis, also gave a negative anti-human globulin consumption test (AGCT).

Group 2 comprises four cases of malignant tumor. Neither a positive LE cell reaction nor a positive LE test was found in this group.

Group 3 comprises 14 cases of parenchymatous diseases of the liver, either hepatitis or cirrhosis. The reason for considering them as a special group is that "false LE cell reactions" have been found quite frequently in these diseases, and that the RA-factor is also found in this group. LE cell reactions were demonstrated in six cases, and one of these also gave a positive LE test and a positive AGCT. While no support for the diagnosis LED could be found in five of the six cases, a diagnosis of LED could not be excluded clinically in the case with the positive LE test, as this was presumably a case of lupoid hepatitis. The case will be discussed in a separate communication.

Group 4 comprises diseases of the blood in the widest sense: haemolytic anaemias, thrombopoenias, forms of purpura, lymphogranulomatosis and macroglobulinaemia. Of the six patients, two had positive LE cell reactions; these were cases of Henoch's purpura and macroglobulinaemia. In none of the cases was the LE agglutination test positive.

Group 5 comprises seven cases with neurological, psychiatric and gastrointestinal diseases. A patient with depressive neurosis had a positive LE cell reaction as the only sign of LED. None of these patients had a positive LE agglutination test.

Group 6 comprises cases with joint symptoms, together with those cases where no more satisfactory diagnosis than collagenosis could be arrived at. There were 26 cases of rheumatoid arthritis, two cases of spondylitis anchylopoëtica, one case of rheumatic fever, one case af periarthritis humeroscapularis, two cases of LED, two cases of myositis, five cases of collagenosis, one case of gouty arthritis, 10 cases of osteoarthritis and three cases of sarcoidosis. All cases of myositis, periarthritis, osteoarthritis, gouty arthritis and spondylitis anchylopoëtica showed both negative LE cell reaction and negative agglutination test. The patient with rheumatic fever had a positive LE cell reaction, but no other sign of LED. Positive antistreptococcal seroreactions and a typical case history confirmed the diagnosis of true rheumatic fever.

Five cases were classified under the vague designations collagenosis or mesenchymosis. Two of these cases showed positive LE cell reactions, but negative agglutination reactions. The one case was a 73-year-old woman, whose main symptoms were muscular pain without actual joint symptoms. The AGCT was only weakly positive, but

the RA-reaction was distinctly positive. The other case was a three-year-old girl with recurrent attacks of fever, accompanied by swelling of the large joints and a non-characteristic exanthema. No incontrovertible diagnosis could be made, but the picture did not resemble LED, and there were no laboratory results which indicated other rheumatic diseases.

Sarcoidosis is usually not included in the group of collagen diseases, but will be mentioned here for practical reasons. All three cases were verified histologically. The one had both a negative LE cell reaction and a negative LE test. Case No. 2 had a typical history with erythema nodosum as presenting symptom; this case showed a positive LE cell reaction, but a negative agglutination reaction. Case No. 3 had both a positive LE cell reaction and a positive LE test. This was a 58-year-old woman, who suddenly developed fever with expectoration. She was sub-febrile for one year, with attacks of fever and migratory joint symptoms. There were also scattered organ signs, including infiltration of the left lung and retinitis with segmented and sheathed vessels and perivascular exudates. During the febrile attacks the various abnormal findings were aggravated. Laboratory studies showed pronounced anaemia, hypersedimentation, elevation of alpha$_2$- and gamma-globulin concentrations and abnormal serum flocculation tests. An immuno-electrophoretic study of the serum proteins showed signs of hyperimmunoglobulinaemia. The sole effective treatment was the administration of adrenocorticosteroids in large doses, a treatment which continued for one year. Her condition then suddenly deteriorated, and tubercle bacilli were now found in the stomach washings. Throughout the entire period of the disease, repeated studies were made for this, but without a positive result. It is presumed that a steroid-activated tuberculosis is involved. As other cases of pulmonary tuberculosis had not shown positive agglutination reactions, and as the clinical picture resembled neither tuberculosis nor sarcoidosis, the histological preparation was re-evaluated, and found to be very strongly suggestive of LED, as the microscopic picture corresponded completely to the lesions described by Teilum (1946): fibrinoid necrosis surrounded by epitheloid cell membranes with scattered giant cells of the Langhans' type.

Among the 26 patients with rheumatoid arthritis, six were found with a positive LE cell reaction (= 23 per cent), but none with a positive agglutination reaction. No other support for the diagnosis of LED was found among these six cases, and it is a well-known phenomenon that in patients with rheumatoid arthritis, positive LE cell reactions are found in up to 25 per cent of the cases (Gsell & Miescher 1959). Therefore, if the rather far-reaching conclusion is to be avoided that LED and rheumatoid arthritis are the same disease, it must be emphasized that the LE cell reaction is not a suitable one for differentiating between these two diseases. On the other hand, the LE test did not give false positive reactions with these patients. In larger patient series, however, the latex agglutination reactions were hardly specific for LED either; the frequency of non-specific reactions using DNA protein was 7 per cent, and using DNA, 22 per cent. The AGCT showed an even higher incidence of non-specific reactions (29 per cent), but this figure included cases of relatively low titre.

Neither is there a possibility of delimiting the two diseases by means of the RA test, as a positive RA test has been found in up to 37 per cent of patients with LED (Fallet, Meyer & Scheidegger, 1961). It is altogether doubtful whether the two diseases can in fact be distinguished by means of serological reactions. Thus Holman (1959) showed that relatives of patients with LED frequently have the RA factor in their blood, even though symptom-free. These findings suggest that such individuals have an abnormal immunological response, which sometimes appears as rheumatoid arthritis, sometimes as LED, and in many cases merely as an abnormal serological reaction.

The two patients with the diagnosis LED will be discussed in detail. Patient No. 1 was a young girl with a typical history and a classic clinical picture. The LE cell reaction, the LE test and the AGCT were all strongly positive, and thus gave no diagnostic difficulties. Case No. 2 had a positive LE cell reaction and an average strength AGCT, but a negative LE test. This was a 64-year-old woman, who in the course of a year in which her chief complaint was increasing muscular weakness in her arms, developed changes in the joints of the hands which were typical of rheumatoid arthritis. At no stage were there any signs of disseminated disease, nor did any general symptoms develop. The diagnosis thus rests only on the two positive reactions, of which we know that both can appear in up to 33 per cent of cases of typical rheumatoid arthritis, so that it is hardly possible to maintain the diagnosis LED.

CONCLUSIONS

The conclusion of the present studies must be that the latex agglutination test is a simple one, with a high specificity and sensitivity for LED. The use of the latex agglutination test as the sole screening test must therefore be considered justifiable. If this simple test had been used in the present material, instead of the LE cell reaction, 27 non-specific reactions would have been avoided, while case No. 2, with doubtful LED, would have been excluded. In the present study, it was not possible to elucidate two circumstances of considerable importance; the behaviour of the reactions in the discoid form of erythematosus, and the behaviour of the reactions during treatment.

Diagnosis:	No. of patients	Positive LE cell reaction	Positive LE test	
Group 1:				
Bronchitis, asthma	2	1	0	
Pericarditis, Pleuritis ..	3	1	0	
Pulmonary tuberculosis	2	1	0	
Pulmonary infiltration	2	1	0	
Infection of the urinary tract	3	2	0	
Lymphocytic meningitis	1	0	0	
Sinusitis	1	0	0	
Continuous fever	1	0	0	
Acute cholecystitis	1	1	0	
Group 2:				
Cancer of the uterus ..	1	0	0	
Cancer of the lungs	2	0	0	
Cancer of the pancreas	1	0	0	
Group 3:				
Cirrhosis of the liver ..	10	4	0	
Chronic hepatitis	2	1	1	(see text)
Acute hepatitis	2	1	0	
Group 4:				
Lymphogranulomatosis .	1	0	0	
Haemolytic anaemia ..	2	0	0	
Purpura	2	1	0	
Macroglobulinaemia ...	1	1	0	
Group 5:				
Gastroduodenitis	1	0	0	
Epilepsy	1	0	0	
Muscular paralysis	1	0	0	
Depressive neurosis ...	1	1	0	
Arteriosclerotic heart disease	1	0	0	
Emaciation	1	0	0	
Pneumothorax	1	0	0	
Group 6:				
Rheumatoid arthritis ..	26	6	0	
Collagenosis	5	2	0	
Myositis	2	0	0	
Rheumatic fever	1	1	0	
Periarthritis	1	0	0	
Spondylitis anchylopoëtica	2	0	0	
Gouty arthritis	1	0	0	
Osteoarthritis	10	0	0	
Sarcoidosis	3	2	1	(see text)
LED	2	2	1	(see text)
Total	100	29	3	

These aspects will be discussed in a subsequent study.

The problem of the applicability of the test to delimit the disease LED, and of the pathogenetic significance of the anti-nuclear factors, is far from solved. It is known with certainty that these factors cannot produce the disease, as newborn children of mothers with LED do not have the disease, in spite of a positive LE cell reaction, nor do animals develop LED after immunization with nucleoprotein. Only one case is known in human pathology where DNA was recognized as the immuno-aetiological factor; the clinical picture was dominated by attacks of urticaria, ecchymoses and ulcerations, without general symptoms. Haematoxylin bodies could be demonstrated in the lesions, but LE cell phenomena could not be demonstrated in the blood. Actual serological studies do not appear to have been made (Levin & Pinkus, 1961). Today, the accepted view would seem to be that the anti-nuclear factors develop in parallel with the disease, and that the disease as such is conditional on the specific mode of reaction of the reticulo-endothelial system in certain individuals. This view receives support from the demonstration of anti-nuclear factors in the serum of a surprising number of the relatives of patients suffering from LED (Pollak, Mandema & Kark, 1960).

SUMMARY

A comparative examination of the diagnostic value of the LE cell phenomenon and the LE agglutination test (Hyland) has been made in 100 patients.

Twenty-nine cases of positive LE cell phenomenon were found, and the diagnosis could be verified in three of them. In 25 of the cases no other support for the diagnosis was found; in one case, the diagnosis was doubtful.

The LE agglutination test gave a positive reaction in the three verified cases of lupus erythematosus. Three were no positive reactions in the remaining 97 cases.

It is concluded that the LE agglutination test is by far superior to the LE cell phenomenon as to specificity and that the sensitivity is adequate.

SUMMARIO

Rob. Jordal e B. Strandberg: UN NOVE SERO-REACTION PRO LUPUS ERYTHEMATOSE DISSEMINATE. *Un comparation inter le test de agglutination de particulas Latex (Hyland) e le phenomeno de cellulas LE.*

Esseva executate in 100 patientes un examination comparative del valor diagnostic del phenomeno de cellulas LE e del test de agglutination LE (Hyland).

Esseva incontrate 29 casos del phenomeno de cellulas LE ex le quales on poteva verificar le diagnose in 3 casos, dum in 25 casos nulle supporto ulterior del diagnose esseva constatate. Le diagnose esseva questionabile in un caso.

Le test de agglutination LE esseva positive in 3 casos verificate de lupus erythematose, negative in le 97 casos restante.

Il es concludite que con respecto a specificitate le test de agglutination LE es multo superior al phenomeno de cellulas LE, e que le sensibilitate es sufficiente.

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PRECOCIOUS SEXUAL DEVELOPMENT

A CLINICAL STUDY OF ONE HUNDRED CHILDREN

SUMMARY OF THESIS

By ERIK THAMDRUP

The series, which has been collected from Danish hospitals and institutions for mental defectives, is delimited arbitrarily to include only patients known to have developed sex characters before their eighth birthday (girls) or ninth birthday (boys).

Table 1.

Classification of Present Series by Aetiology or Signs.

Clinical type	Girls	Boys	Total	
True precocious puberty				
Without cerebral disease (constitutional)	34	4	38	> 56
With cerebral disease	11	7	18	
Adrenogenital syndrome				
Hyperplasia	10	5	15	> 17
Tumour	2	—	2	
Gonadal tumours				
Granulosa-cell tumour of the ovary	1	—	1	> 2
Interstitial-cell tumour of the testis	—	1	1	
Premature pubarche				
Without cerebral disease (constitutional?)	3	2	5	> 17
With cerebral disease	9	3	12	
Premature thelarche				
Without cerebral disease (constitutional?)	4	—	4	> 6
With cerebral disease	2	—	2	
Unclassifiable (exogenous hormonal action?)	2	—	2—2	
Total	78	22	100	

Table 1 gives the distribution of the cases according to sex and to aetiology or symptomatology. Sexual precocity is much commoner in girls than in boys. This sex distribution is especially evident in the group true precocious puberty.

True precocious puberty is defined as abnormally early pubertal development which does not differ, apart from its early onset, from normal pubertal development. The patients of this group are divided into a constitutional (or idiopathic) and a cerebral type, differing only in the presence of brain lesions in the latter.

In a total of 45 girls and 11 boys the premature sexual development was interpreted as true precocious puberty. Of these, 11 girls and seven boys had brain lesions.

Most of the patients were seen at such brief intervals that the age at onset of the individual sex characters could be recorded. As a rule, the rate of development was faster, though in a few cases slower, than in children whose puberty begins at the normal age. The distribution of the patients in the constitutional group by age at onset of pubertal development and at menarche supports the theory that the pubertal development in these cases may be explained by the scatter that may occur with any physiological process.

Three girls had ovarian cysts. Extirpation of the cystic ovary, done in one case, did not alter the signs. A review of the reported cases of ovarian cysts in girls with precocious puberty supports the view that these cysts are not the cause, but the result of the premature pubertal development. Therefore, oophorectomy should not be done.

Histological examination of endometrial biopsies revealed signs of ovulation in five out of eight girls.

Longitudinal growth and osseous development were accelerated in all the patients. In 34 followed until after cessation of growth, the longitudinal growth was arrested between nine and 14 years of age. A few had attained an approximately normal stature and normal body proportions, but 10 of the female and two of the male patients were under 150 cm and the ratio upper segment/lower segment was in most cases as in children of 5—9 years. The circumference of the head in the full-grown patients was strikingly large. The following factors appear to decide the final stature: The earlier the onset of pubertal development and the faster its course, the sooner will growth be arrested by early epiphyseal fusion. However, hereditary factors also appear to influence the final stature.

The urinary excretion of hormones was investigated in 54 cases. Gonadotrophic hormone was demonstrated in eight, but nearly all the investigations were performed by a method which does not permit a detailed quantitative evaluation. The excretion of neutral 17-ketosteroids and reducing corticoids was in most cases in excess of the normal average for their chronological age, but was evenly distributed around the average for their bone age. Fractionation of 17-ketosteroids showed in two boys with hypothalamic tumours increased excretion of the dehydroisoandrosterone fraction. Thus, the tumours appear to have induced not only increased gonadal function, but also hyperfunction of the adrenal cortex. Biological tests disclosed urinary oestrogen and an-

drogen in all cases where the investigations were performed at least two years after the onset of pubertal development. The results of hormonal studies carried out after the completion of pubertal development indicate that at an adult age a number of the patients have rather low adrenocortical function and a few of them also hypofunction of the gonads.

X-rays of the sella turcica showed its size, in terms of the area of the median sellar profile, to be within the normal range for the chronological age in nearly all cases who did not have increased intracranial pressure. X-rays of the urinary tract and adrenal regions showed anomalies of the urinary tract in about 10 per cent of the X-rayed cases, an incidence of the same order of magnitude as in nonselected autopsy series.

Eighteen patients (11 girls and seven boys) with true precocious puberty had brain lesions. Their case histories are reported. Four had hypothalamic tumours, two tuberose sclerosis, one cystic arachnoiditis, three congenital internal hydrocephalus with signs of increased intracranial pressure, four atrophic encephalopathy without pressure symptoms, and four cryptogenic epilepsy. Autopsy, operation, or air encephalography showed the hypothalamic region to be involved in the brain lesion in 11 of the 18 cases. Another three had such severe brain lesions that very probably the hypothalamic region was involved.

Electroencephalography in 15 cases without signs of brain lesions revealed a predominant alpha frequency normal for the patients' chronological age. Thus, early biological maturation does not appear to entail a more adult (faster) alpha rhythm.

It is reasonable to maintain the term *constitutional* precocious puberty for cases without brain lesions, since there is a distinct preponderance of close female relatives with very early menarche among the patients of this group as compared with the patients of the other groups of the present series. Five out of 37 (14 per cent) mothers of patients with true precocious puberty without brain lesion had their menarche before their 12th birthday as against 4.5 per cent in the general population.

Intellectual development in children with true precocious puberty without brain lesion corresponded to their chronological age. Their intelligence quotients were distributed according to a Gaussian curve as in the general population.

Nearly all the parents worried over the children's sexual activity, but only a few could base their worries on concrete episodes. Only two children, both with brain lesions, had been sexually aggressive and only for a time. Nine patient have been followed after the age of 16. The oldest two, who were 36, were married and had children. Several of the adult patients were inhibited in their sexual activity by feelings of inferiority because of their short stature and peculiar body proportions.

Seventeen patients (12 girls and five boys) had the *adrenogenital syndrome*. In eight of the girls and in all five boys the hypercorticism was due to congenital adrenocortical hyperplasia, in two girls to postnatal adrenocortical hyperplasia, while two girls had adrenocortical adenomas.

Two of the patients with congenital adrenocortical hyperplasia were siblings. After the study was concluded, congenital adrenocortical hyperplasia has been observed among younger siblings of another two patients.

In two of the girls with congenital adrenocortical hyperplasia the virilization of the external genitalia was so pronounced that for a time they were thought to be boys with undescended testes and hypospadias. Four of the patients with congenital adrenocortical hyperplasia had shown breast development for a few months in the range 7½ to 10 years, and in two of them the breast development returned when menstruation set in at the ages of 12 and 27 years.

Two girls with postnatal adrenocortical hyperplasia had normal external genitalia. Pubic hair appeared in both at the age of 5—6 years. The hypercorticism was not recognized until a marked increase in the 17-ketosteroid excretion occurred at the time of normal pubertal development in the age range 12—16 years.

Longitudinal growth and osseous development were accelerated in the majority of cases, but normal in a 4-year-old girl with adrenocortical tumour and in a 7-month-old boy with congenital adrenocortical hyperplasia. The explanation in these two cases is probably that they were examined at a very early stage of the disease. Longitudinal growth was accelerated, but osseous development normal in a girl with postnatal adrenocortical hyperplasia. After cessation of growth the height was 144 to 151 cm in five out of seven patients with congenital adrenocortical hyperplasia. They had relatively short limbs and large heads. Two girls with postnatal adrenocortical hyperplasia attained an almost normal average height.

Urinary excretion of neutral 17-ketosteroids was elevated in all the tested cases, not only in relation to chronological but also to bone age. Cortisone therapy normalized the 17-ketosteroid excretion in 10 patients with adrenocortical hyperplasia, but failed to affect the excretion in one patient with adrenocortical tumour. The excretion of reducing corticoids was considerably increased in most cases.

The size of the sella turcica, assessed on the basis of the area of the median sellar profile, was normal for the patients' chronological age.

Intravenous pyelography disclosed adrenal tumours in two cases, in one of them not until the investigation had been supplemented by tomography of the adrenal regions.

Seven of eight patients with adrenocortical hyperplasia who had oral glucose tolerance tests showed a fairly low sugar tolerance.

The predominant alpha frequency in the electro encephalogram was strikingly fast in one out of nine patients, while in the others it corresponded to the patients' chronological ages.

One of the two patients with adrenocortical tumour died of postoperative adrenocortical insufficiency. In the other one, the hormone excretion returned to normal and the sex characters regressed partially after removal of the tumour.

Six female and three male patients with adrenocortical hyperplasia are now on continuous cortisone medication. This had normalized the urinary excretion of hormones and, in the youngest patients, the longitudinal growth. In the female patients the treatment has entailed complete or partial regression of the virilizing signs and, in the oldest patients, appearance of breast and menstruation. Normal pubertal development began unusually early in two girls and two boys whose bone ages ranged from 10 to 14 years at the commencement of the medication.

In the case of one girl with congenital adrenocortical hyperplasia. who had been mistaken for a boy, the "sex was changed" at the age of two years. In the case of another girl with congenital adrenocortical hyperplasia who had been reared as a girl until the age of nine years, the "sex was changed" to male. At the age of 27 this patient developed breasts and mentrual periods. Since the patient is still living as a man, hysterectomy and mastectomy were performed.

Hormone-producing gonodal tumours are extremely rare in children, especially in boys. The present series include one girl with granulosa-cell tumour and one boy with interstitial-cell tumour. Surgical removal of the tumours was followed by complete regression of the sex characters in the girl and partial regression in the boy. In the girl the urinary excretion of hormones had not been investigated prior to the operation, but after the operation it has been normal. In the boy, the 17-ketosteroid excretion dropped from 40.1 mg/24 hours before to normal values after the operation. The remaining testis underwent considerable enlargement, explicable either as compensatory hypertrophy or as early onset of normal pubertal development, since the patient's bone age at the time of operation was 12½ years.

Premature pubarche (isolated premature development of sexual hairing without other signs of incipient pubertal development) was found in 17 cases, 12 girls and five boys. Severe brain lesions, congenital or acquired early (in connection with birth) were found in nine of the girls and in three of the boys.

In patients without brain lesions, the premature development of sexual hairing appears to be explicable by a slightly increased adrenocortical production of androgen, since the 17-ketosteroid excretion in these cases was fairly high and their longitudinal growth as well as osseous development was slightly accelerated. The patients with brain lesions, on the other hand, did not show signs of increased androgen production, their 17-ketosteroid excretion being as a rule normal or reduced and their longitudinal growth as well as osseous development retarded. The premature development of sexual hairing in these patients is perhaps due to an abnormality of the follicles of the sexual hairs.

The striking frequency of brain lesions among children with premature pubarche does not appear to be due to chance, since among 393 non-selected mentally deficient children premature development of sexual hairing was found in eight, all of whom had severe organic brain lesions.

Premature thelarche (isolated premature development of the breasts without other signs of beginning pubertal development) was observed in six girls, two of whom had brain lesions. In two of the patients the mammary hyperplasia regressed completely in 6—9 months. Longitudinal growth and osseous development were normal in all cases. The 17-ketosteroid excretion was slightly elevated in one case and the corticoid excretion in another while in the remaining cases the excretion of these substances was normal. None of the patients had oestrogenic hormone in the urine or oestrogenization of the cells of the vaginal epithelium. It is doubtful, whether the breast development and brain lesions were pathogenetically related in the two patients with brain diseases. Investigation of 122 mentally deficient girls under eight years of age did not disclose breast development in any case. Since three of the present patients had shown mammary hyperplasia at birth, there is probably a pathogenetic relationship between neonatal mammary hyperplasia and premature thelarche: Hypersensitivity of the mammary tissue to oestrogenic hormone, perhaps of constitutional nature, seeing that two of the patients were sisters.

The premature development of sex characters in two of the girls of the present series is best explained by an *exogenous action of oestrogen-containing drugs.* Both had slight breast development and pubic hairing and, especially one of them, pronounced pigmentation of the areolae and nipples. One of the patients had a single vaginal bleeding. All signs regressed spontaneously in both cases within six months.

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ECZEMATOUS ALLERGY TO BALSAMS, PERFUMES AND FLAVOURING AGENTS

SUMMERY OF THESIS

By NIELS HJORTH

About one half of all allergic eczemas are caused by sensitivity to ointments or other externally applied remedies. To a large extent, changes in the frequency of sensitivity reactions to various remedies reflect changes in the prescribing habits of the medical profession. However, the frequency of sensitivity to balsam of Peru has remained high throughout the years with only slight fluctuations, although balsam of Peru must be regarded as obsolete from a medical point of view.

This sensitivity was formerly considered as a curiosity of no practical significance. However, the unchanging frequency of cases over the years must raise the following questions: 1) How are patients sensitized to balsam of Peru, 2) which components of balsam of Peru give rise to allergic reactions, and 3) what are the consequences of this sensitization. The investigation was extended to include a number of other resins and several other aromatic compounds not formerly examined collectively in the dermatological literature.

It was to be expected that sensitization to a natural product as complex as balsam of Peru designated as "crossensitivity" or "group sensitivity to one substance frequently involves other closely related substances; this phenomenon is designated as "crosssensitivity" or "group sensitization". Balsam of Peru contains benzyl benzoate, several other derivatives of benzoic acid, cinnamic acid and small amounts of vanillin. Resins of unknown composition constitute thirty to forty per cent of the balsam.

Balsam of Peru is used in various ointments, such as vaselinum balsami peruviani Ph. Dan., vaselinum benzocaini balsamicum Ph. Dan., chilblain ointments, suppositories for haemorrhoids, formerly in Jelonet® and still in throat lozenges. It is also used in the cosmetic industry *(e. g.* in lipstick perfumes) and in the flavouring industy.

The clinical investigation was undertaken in the years 1954 to 1959 and comprised a total of 230 patients who had given positive reaction to patch test with balsam of Peru, 25 per cent in lanolin. Forty-six per cent of the patients had hand eczema, 26 per cent leg eczema. No less than 84 per cent had had eczema previously.

One hundred and eighty-two patients were questioned closely as to previous use of balsam of Peru. Of these, 126 (69 per cent) remembered having used balsam of Peru in some form previously, in half the cases for burns. One hundred and eleven of the 126 had used the "perubalsam vaselin" of the Danish pharmacopoea. This proportion, however, appears to disagree with the results of a questionnaire sponsored by the Association of Danish Pharmaceutical Chemists, according to which only 50 to 60 per cent of the balsam of Peru purchased by the chemists is used for "perubalsam vaselin". It may thus be assumed that the majority of Danish patients have been sensitized by therapeutic use of balsam of Peru, and not by the use of substances such as vanillin, cinnamon or perfumes containing balsams.

The sensitizing components in balsam of Peru.

Some 50 per cent of the patients reacted to one or more of the known constituents of balsam of Peru, *e. g.* cinnamic acid, benzoic acid, benzyl benzoate, etc. These sensitivities, however, varied from one patient to another, and as half of the patients examined showed negative reactions, the sensitivity to balsam of Peru must be assumed to be caused rather by non-isolated fractions of the balsam. Fractionation by means of various solvents showed in fact that the most active constituents were concentrated in a resinous fraction, amounting to approximately 3 per cent of the balsam.

A micromethod of column chromatography was evolved for further study. Two strongly eczematogenic fractions were isolated by this method, one a resin identical with that mentioned above, while the other contained the specific odoriferous constituents. All the patients reacted to the resinous fraction, some of them also to the odoriferous components. In perfumery, it is possible to use resin-free balsam of Peru, which is thus less eczematogenic than the balsam used pharmaceutically.

It has been impossible to isolate the individual components of balsam of Peru resin because of their tendency to spontaneous oxidation and polymerization. They are assumed to consist of esters of a so-called coniferyl alcohol, the benzoic acid ester of which may be isolated from another resin, Siam benzoin. Coniferyl benzoate gave stronger reactions than any other pure compound included in the investigation, which demonstrates that esters of coniferyl alcohol must be the most important allergens in balsam of Peru resin. Later experiments confirmed that coniferyl benzoate is strongly sensitizing in both human subjects and guinea-pigs.

Consequences of sensitization to balsam of Peru.

The extended investigation comprised numerous other pure aromatic compounds, chemically

related to the known individual components of balsam of Peru. It was shown that patients sensitive to balsam of Peru with hardly any exception reacted to one or more compounds *not* occurring in balsam of Peru. These compounds, such as derivatives of cinnamic alcohol, benzyl alcohol and eugenol, occur in spices, fruits and perfumes. Sensitivity to the compounds investigated is extremely rare among all other eczema patients.

Similarly, sensitivity to some other balsams and resins was a frequent finding (balsam of Tolu, styrax and benzoin); these are used in perfumes and, especially in other countries, for therapeutic purposes.

Perfumes or cosmetics were frequently the cause of eczema in female patients. Many of them do not use "scent", but are nevertheless in daily contact with perfumes through toilet soaps. In order to estimate the practical significance of the cross-sensitivity to perfumery chemicals, patch tests were performed with the perfumes from the most popular toilet soaps, which contain between 0.5 and 1 per cent perfume. The investigation comprised five brands, two of which are supposed to cover between 30 and 50 per cent of the Danish consumption of toilet soap. Positive reactions to one or more brands were found in 50 per cent of 115 patients sensitive to balsam of Peru. On the other hand, among 336 other patients with eczema of hands and face, only 2 per cent were found with positive reactions to these perfumes. This shows that toilet soap perfumes are in themselves "hypoallergenic", *i. e.* with a low sensitizing potential, but that sensitization to balsam of Peru involves sensitivity to chemicals or natural products commonly used for toilet soap perfumes. An analysis of the results of the investigation showed that two of the perfumes in fact must contain styrax or closely related compounds.

The investigation was further extended to fruits and spices, as possible causes of ezcema, either by contact or by ingestion. As balsam of Peru contains derivatives of cinnamic acid and vanillin, it might be expected that a number of patients would be sensitive to cinnamon and vanilla, which indeed was the case. The cross sensitivity to vanilla was, however, not dependent on vanilla but on some resinous components of vanilla. The final analysis of the material revealed a strikingly large number of patients with orange peel eczema. Supplementary investigations showed the existence of cross sensitivity between the resins in orange peel and balsam of Peru.

The development and persistence of sensitivity to balsam of Peru.

Sensitivity to balsam of Peru probably persists throughout life, although in some patients it may decrease gradually in degree over the years. However, patients sensitive to balsam of Peru are particularly liable to develop new sensitivities to aromatic compounds, for example perfumes and spices. The investigation would appear to confirm the following universal rule: established sensitivity to one compound predisposes to the development of sensitivity (and eczema) from contact with chemically related substances.

Concluding Remarks.

Sensitization to balsam of Peru involves sensitivity to numerous substances, to which everyone is exposed in everyday life. Where the resistance of the skin is broken down by other factors, e. g. housework, the sensitivity to balsam of Peru may be the decisive factor in the development of clinical eczema. Thus, development of eczema of the hands may appear immediately after the use of balsam of Peru for the treatment of burns in other regions. The explanation is probably that sensitization caused by the treatment leads to sensitivity to toilet soap perfumes, orange peel, etc., with subsequent eczema localized to the hands.

The sensitization comprises a number of substances occurring in food-stuffs (orange peel, spices, etc.) and medicaments (throat lozenges, etc.). The ingestion of such products can presumably elicit or maintain eczema in a patient sensitive to balsam of Peru.

The majority of the patients in the present material were sensitized by use of the 10 per cent "perubalsam vaselin" of the Danish pharmacopoea.

The demand for such a remedy, sold over the counter, will hardly be affected by its deletion from the Danish pharmacopoea. Since the risk of sensitization from an ointment is largely dependent on the concentration of the active ingredient, a reduction of this concentration will be the most effective measure for reducing the frequency of sensitivity to balsam of Peru.

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